Antithrombotic therapy use in patients with atrial fibrillation before the era of non-vitamin K antagonist oral anticoagulants: the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phase I cohort

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Aims	The introduction of non-VKA oral anticoagulants (NOACs), which differ from the earlier vitamin K antagonist (VKA) treatments, has changed the approach to stroke prevention in atrial fibrillation (AF). GLORIA-AF is a prospective, global registry programme describing the selection of antithrombotic treatment in newly diagnosed AF patients at risk of stroke. It comprises three phases: Phase I, before the introduction of NOACs; Phase II, during the time of the introduction of dabigatran, the first NOAC; and Phase III, once NOACs have been established in clinical practice.
Methods and results	In Phase I, 1063 patients were eligible from the 1100 enrolled (54.3% male; median age 70 years); patients were from China (67.1%), Europe (EU; 27.4%), and the Middle East (ME; 5.6%). The majority of patients using VKAs had high stroke risk (CHA$_2$DS$_2$-VASc ≥ 2; 86.5%); 13.5% had moderate risk (CHA$_2$DS$_2$-VASc = 1). Vitamin K antagonist use was higher for persistent/permanent AF (47.7%) than that for paroxysmal (23.9%). Most patients in China were treated with antiplatelet agents (53.7%) vs. 27.1% in EU and 28.8% in ME. In China, 25.9% of patients had no antithrombotic therapy, vs. 8.6% in EU and 8.5% in ME.
Conclusion	Phase I of GLORIA-AF shows that VKAs were mostly used in patients with persistent/permanent (vs. paroxysmal) AF and in those with high stroke risk. Furthermore, there were meaningful geographical differences in the use of VKA therapy in the era before the availability of NOACs, including a much lower use of VKAs in China, where most patients either received antiplatelet agents or no antithrombotic treatment.
Keywords	Atrial fibrillation • Stroke • Oral anticoagulation • Registry

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What's new?

- GLORIA-AF is a prospective, long-term global registry in non-valvular atrial fibrillation (AF) with three separate phases: Phase I, baseline cohort before the introduction of non-VKA oral anticoagulants (NOACs); Phase II, just after the introduction of the first NOAC dabigatran, with 2-year follow-up in dabigatran-treated patients; and Phase III, 3-year follow-up study in patients on any antithrombotic treatment.

- In this Phase I part of GLORIA-AF, before availability of NOACs, vitamin K antagonists (VKAs) were mostly used in patients with persistent/permanent (vs. paroxysmal) AF, and in those with high stroke risk.

- Compared with the rest of the world, VKA use is much lower in China, where most patients were either treated with antiplatelet agents or received no antithrombotic treatment.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects ~1–2% of the adult population.[1] The lifetime risk for development of AF is one in four for those over the age of 40 years.[2] The prevalence of AF rises with advancing age, increasing from <1% in those <60 years of age to nearly 20% in those 85 and older.[3] Thromboembolic complications—particularly ischaemic stroke and systemic thromboembolism—are a major cause of morbidity and mortality in patients with AF. Patients with AF have a four- to five-fold higher risk for stroke than those without AF.[4–6] Up to 15% of all strokes are due to AF, and strokes in patients with AF have worse outcomes with higher mortality rates than strokes in patients without AF.[7]

Until recently, the treatment choices for stroke prevention in patients with AF were vitamin K antagonists (VKAs, e.g. warfarin) or antiplatelet agents such as aspirin [acetylsalicylic acid (ASA)]. A meta-analysis demonstrated that warfarin decreased the risk of stroke/systemic embolism on average by 64% vs. placebo (all-cause mortality by 26%), while antiplatelet therapy reduced the occurrence of stroke by 22% vs. placebo. When the analysis was confined to the ASA-only studies, ASA reduced stroke by 19% (95% confidence interval, −1 to 35%) vs. placebo,[8,9] with no reduction in mortality.

The benefits of VKAs must be weighed against important limitations including a narrow therapeutic window, an unpredictable dose−response, numerous drug−drug and drug−food interactions, and a slow onset and ebbing of action.[10] As a result, many patients with AF do not receive VKAs, but receive ASA, antiplatelet agents, or both, or no antithrombotic therapy.[4] With the approval of non-VKA oral anticoagulants (NOACs), including thrombin inhibitors such as dabigatran etexilate (dabigatran) and factor Xa inhibitors such as rivaroxaban and apixaban for stroke prevention in patients with non-valvular AF (NVAF), antithrombotic treatment patterns have changed.

In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, which was the first Phase III study in patients

with NVAF, dabigatran 150 mg twice daily was demonstrated to be superior to warfarin, while dabigatran 110 mg twice daily was shown to be non-inferior to warfarin for the prevention of stroke and systemic emboli. The higher dose of dabigatran was associated with comparable risk of major bleeding, whereas the lower dose was associated with fewer major bleeds. Importantly, both doses of dabigatran etexilate considerably reduced the occurrence of intracranial haemorrhage vs. warfarin.[11]

After drug approval, additional collection of data from clinical practice is essential to characterize the broad spectrum of co-morbidities and other medication use and to understand antithrombotic treatment patterns and responses outside the more controlled setting of clinical trials. Analyses of claims and electronic medical record data, such as the recent analysis of Medicare data for dabigatran etexilate,[12] enable rapid and early evaluation of outcomes; however, to collect accurate, pertinent information and to allow for the adequate control of confounding factors, new data should ideally be pursued. A prospective registry enables precise collection of important baseline information in patients managed in the course of routine care (e.g. smoking, alcohol use, and co-medication, including platelet inhibitors).

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) was designed to provide prospective information on a population with recently diagnosed AF. In this article, results from the Phase I cohort of GLORIA-AF are presented, including baseline characteristics and initial antithrombotic management of patients before the approval of NOACs.

Methods

The design of the GLORIA-AF Registry Programme has been reported previously.[13] Briefly, GLORIA-AF is an ongoing disease registry of newly diagnosed AF patients run in three separate phases, as follows. In Phase I, conducted before approval of the first NOAC, information has been collected on prescription patterns prior to availability of NOACs on the market. This initial phase used a cross-sectional approach, with no data collected beyond the initial visit. Phase I was conducted only in countries that had not yet received marketing authorization at the time of study initiation; this design therefore limited the participating countries and the enrolment time for entering patients.

Patients

Patients aged ≥18 years with newly diagnosed (≤3 months before the baseline visit) NVAF and at risk for stroke (CHA$_2$DS$_2$-VASc score ≥1) were included. A broad cross-section of consecutively examined patients, treated within the different healthcare settings of each participating country, was included (e.g. general practices, specialist offices, community hospitals, and university hospitals).

Patient symptom burden categories reflect the European Heart Rhythm Association classification.[14] Patients were categorized as symptomatic (defined as severe or disabling symptoms that impact daily activities), minimally symptomatic, or asymptomatic.

Patients were excluded if they had (i) mechanical heart valves or valve disease expected to require valve replacement, (ii) received >60 days of VKA treatment in their lifetime for any indication, (iii) AF with a generally reversible cause, (iv) expected life expectancy <1 year at the time of enrolment as assessed by the investigator, or (v) a medical condition other than AF for which chronic use of VKAs was indicated. Patients

receiving NOACs were excluded when analysing predictors of VKA use and reasons to forego VKAs.

As Phase I was conducted before approval of the first NOAC, at the time of study initiation, this design restricted country participation, and hence inclusion of patients, to the following: China, The Netherlands, Spain, Germany, Croatia (defined as Europe), Egypt, Lebanon, Turkey, and the United Arab Emirates (defined as the Middle East). At the cross-sectional (or baseline) assessment, clinical and demographic characteristics were recorded, as were type of AF and management approaches.

Data quality control

An academic steering committee designed and provided scientific oversight of all phases of the programme. Regular meetings of the study team and the chair and co-chairs of the steering committee were held throughout the study.

Data were collected in electronic case report forms, and investigators were trained on the electronic data capture system before entering any data. Data quality was monitored electronically as well as through periodic medical and data quality reviews, on-site monitoring, and audits. Investigators were asked to enrol all eligible patients consecutively to limit selection bias at the patient level.

Statistical analysis and study size

For Phase I, data were summarized descriptively, displaying median and interquartile ranges [IQR; given by Q1 (25% quartile) and Q3 (75%)] for continuous variables. Categorical variables were expressed as frequencies and percentages. Statistical analysis was performed using SAS software version 9.2 (SAS Institute Inc.).

For summary of data by antithrombotic therapy, similar treatment regimens were pooled for analysis, resulting in the following four treatment groups, which had been available in the respective time period: (i) VKA, defined as treatment with VKAs alone or in combination with other antiplatelet medications; (ii) ASA, defined as treatment with ASA alone or in combination with other antiplatelet medications; (iii) antiplatelet agents other than ASA, defined as treatment with single or combination antiplatelet medications; and (iv) no treatment. A category 'missing' is shown whenever at least one patient with missing data occurred.

Main predictors for VKA use were identified based on multivariable logistic regression analysis using the backward model selection procedure. Sensitivity analyses were conducted using stepwise selection and based on a broader model including relevant covariates based on the results seen in univariable regression. Odds ratios and corresponding 95% confidence intervals are presented.

End of Phase I and thereby overall study size was driven—per the study design—by approval and availability of dabigatran within a country.

Results

From May 2011 (date of first patient in) until January 2013 (date of last patient in), 1100 patients from 64 centres were enrolled in Phase I of the registry; 59 of the centres enrolled at least one eligible patient. Of the enrolled patients, 1063 were eligible for inclusion in the analysis of the Phase I data; for the 37 patients who were not eligible, the most frequent reasons for exclusion were inclusion after the study stop date ($n = 15$) and informed consent before the site initiation visit ($n = 15$). Patients were included from China (67.1%), Europe (27.4%), and the Middle East (5.6%). The majority of eligible patients (95.2%; $n = 1012/1063$) were enrolled by cardiologists, and the type of participating centres can be seen in *Table 1*.

Table I Enrolling centres

	Number of sites, *n* (%)[a]
Total	59 (100)
Type of site	
General practice/primary care	4 (6.8)
Specialist office	14 (23.7)
Community hospital	2 (3.4)
University hospital	36 (61.0)
Outpatient healthcare centre	0 (0.0)
Anticoagulation clinic	0 (0.0)
Other	3 (5.1)

[a]Only sites with at least one eligible patient are displayed.

Of the 1063 enrolled patients (median age 70 years [IQR, 61.0–77.0]; 45.7% female), 74.8% (795) had hypertension, 22.6% (240) diabetes mellitus, and 24.1% (256) congestive heart failure. Further demographics and co-morbidities are summarized in *Table 2*.

The majority of patients overall had symptomatic AF (62.2%; 661/1063), with higher frequency in China (64.8%; 462/713) and in the Middle East (64.4%; 38/59) than in Europe (55.3%; 161/291). Asymptomatic AF was more frequent in Europe (24.1%; 70/291) than in China (13.5%; 96/713) and the Middle East (8.5%; 5/59) (*Figure 1*).

Stroke and bleeding risk scores

Overall, 54.1% of patients had a high stroke risk (CHADS$_2$ score $\geq$2). The median (Q1, Q3) CHADS$_2$ score was 2.0 (1.0–3.0) and the median (Q1, Q3) CHA$_2$DS$_2$-VASc score was 3.0 (2.0–4.0). The median (Q1, Q3) HAS-BLED risk score was 1.0 (1.0–2.0). Overall, the majority (80.9%; 860/1063) of patients had low bleeding risk (HAS-BLED score $<$3). The stroke and bleeding risk score classes per region are summarized in *Table 3*.

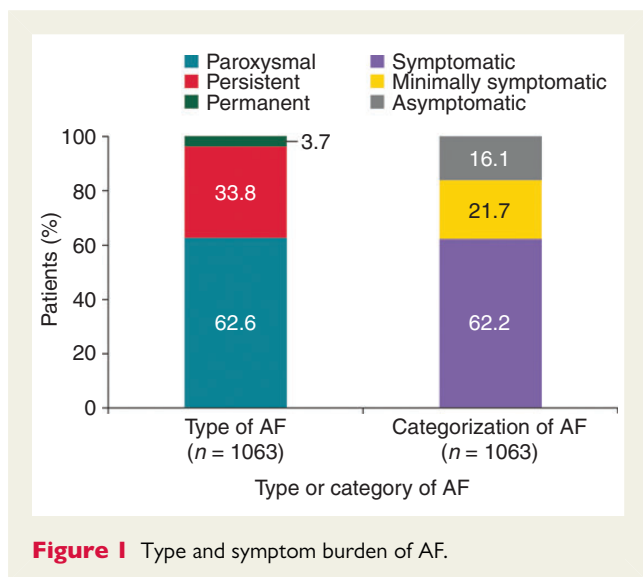## Selection of antithrombotic therapy

Overall, of the 1063 patients, treatment with ASA was the most common at 41.7% of patients (443), followed by 32.8% (349) treated with VKAs and 3.4% (36) treated with antiplatelet agents other than ASA; 20.2% (215) did not receive antithrombotic therapy. The remaining 1.9% of patients (20), comprising 1 patient from Europe and 19 from the Middle East, received a NOAC in various treatment combinations. When assessing antithrombotic treatment choice by region, treatment with VKAs was more common in Europe than in China. Treatment with ASA or no antithrombotic treatment was more common in China than in Europe (*Figure 2*).

Overall, among the 1063 eligible patients, VKA monotherapy was more common (24.1%; $n = 256$) than VKAs in combination with a single antiplatelet agent (7.8%; 83) and with multiple antiplatelet agents (0.9%; 10). Similarly, ASA monotherapy was more common (30.4%; 323) than ASA in combination with other antiplatelet agents (11.3%; 120). Similar patterns in monotherapy were observed within regions. Vitamin K antagonist combination therapy was most frequently ASA. Excluding combinations with VKAs, ASA combination

Table 2 Patient demographic and baseline characteristics

Characteristic	China (n = 713)	Europe (n = 291)	Middle East (n = 59)	Total (n = 1063)
Age, median, years (Q1, Q3)	69 (59, 77)	71 (64, 79)	65 (57, 74)	70 (61–77)
Female, n (%)	305 (42.8)	147 (50.5)	34 (57.6)	486 (45.7)
BMI, median, kg/m^2 (Q1, Q3)	23.9 (21.5, 26.1)	28.1 (25.4, 31.2)	27.3 (24.2, 33.3)	25.0 (22.5–28.0)
Medical history, n (%)				
Previous stroke	73 (10.2)	31 (10.7)	6 (10.2)	110 (10.3)
Myocardial infarction	59 (8.3)	32 (11.0)	8 (13.6)	99 (9.3)
Coronary artery disease	181 (25.4)	59 (20.3)	16 (27.4)	256 (24.1)
Congestive heart failure	176 (24.7)	65 (22.3)	15 (25.4)	256 (24.1)
History of hypertension	500 (70.1)	248 (85.2)	47 (79.7)	795 (74.8)
Diabetes mellitus	139 (19.5)	79 (27.1)	22 (37.5)	240 (22.6)
Chronic GI diseases	61 (8.6)	9 (3.1)	3 (5.1)	73 (6.9)
Type of AF				
Paroxysmal	470 (65.9)	155 (53.3)	40 (67.8)	665 (62.6)
Persistent	231 (32.4)	115 (39.5)	13 (22.0)	359 (33.8)
Permanent	12 (1.7)	21 (7.2)	6 (10.2)	39 (3.7)
AF ablation	34 (4.8)	3 (1.0)	0 (0.0)	37 (3.5)
Any drug (HAS-BLED)	406 (56.9)	147 (50.5)	32 (54.2)	585 (55.0)

AF, atrial fibrillation; BMI, body mass index; GI, gastrointestinal; Q1, 25%-quartile; Q3, 75%-quartile.

Figure 1 Type and symptom burden of AF.

therapy with clopidogrel was the most common. A few patients (3.4%; 36) were treated with antiplatelet agents other than ASA.

Antithrombotic treatment by atrial fibrillation type

The majority of patients had paroxysmal (62.6%) or persistent AF (33.8%), and most were symptomatic (62.2%) or minimally symptomatic (21.7%). When assessing the treatment per type of AF, patients with paroxysmal AF were predominantly treated with ASA, whereas patients with persistent and permanent AF were predominantly treated with VKAs (*Figure 3*).

Stroke risk by treatment

When assessing treatment pattern per stroke risk scores, patients with high risk (CHADS$_2$ score $\geq$2) comprised the majority of patients in groups that received treatment: 61.3% (214/349) on VKA treatment, 56.7% (51/443) on ASA treatment, and 75.0% (27/36) on antiplatelet agents other than ASA. Nevertheless, 33% of patients receiving no antithrombotic treatment had a CHADS$_2$ score $\geq$2, and 22.3% of Chinese patients with a CHA$_2$DS$_2$-VASc $\geq$2 received no antithrombotic treatment. Of the 215 patients with no treatment, according to CHADS$_2$ risk score, 50.7% (109) had a moderate risk and 16.3% (215) had a low risk score of 0.

For high stroke risk patients in China (CHA$_2$DS$_2$-VASc $\geq$2), there was still a large proportion receiving only ASA (52.0%) or no therapy (22.3%) (*Figure 4*). In Europe and the Middle East, high stroke risk patients (CHADS$_2$ score $\geq$2) received ASA in 18.3% (33/180) and 22.2% (8/36) or no therapy in 3.9% (7/180) and 8.3% (3/36), respectively.

Bleeding risk by treatment

In the VKA group, the majority of patients (84.2%) had a low HAS-BLED risk score (HAS-BLED <3), vs. 76.5% in the ASA group and 63.9% in the antiplatelet agents other than ASA-treated group. Of the patients without antithrombotic treatment, 89.8% were classified as low bleeding risk.

Predictors for vitamin K antagonist use

Based on the multivariable logistic regression analysis, the most relevant predictors for VKA use were AF ablation, region, any drugs causing bleeding [i.e. antiplatelet agents and/or non-steroidal anti-inflammatory drugs (NSAIDs)], non-central nervous system (CNS) arterial embolism, and hepatic disease (see *Table A1* in the

Table 3 Stroke and bleeding risk scores

	China (n = 713)	Europe (n = 291)	Middle East (n = 59)	Total (n = 1063)
$CHADS_2$ score class, n (%)				
Low (score = 0)	84 (11.8)	16 (5.5)	2 (3.4)	102 (9.6)
Moderate (score = 1)	270 (37.9)	95 (32.6)	21 (35.6)	386 (36.3)
High (score ≥ 2)	359 (50.4)	180 (61.9)	36 (61.0)	575 (54.1)
CHA_2DS_2-VASc score class, n (%)				
Score = 0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Score = 1	184 (25.8)	36 (12.4)	6 (10.2)	226 (21.3)
Score ≥ 2	529 (74.2)	255 (87.6)	53 (89.8)	837 (78.7)
HAS-BLED score class, n (%)				
Low (score < 3)	596 (83.6)	224 (77.0)	40 (67.8)	860 (80.9)
High (score ≥ 3)	88 (12.3)	23 (7.9)	10 (16.9)	121 (11.4)
Missing	29 (4.1)	44 (15.1)	9 (15.3)	82 (7.7)

$CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke (doubled); CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65−74 years, sex category (female); HAS-BLED, hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (e.g. age >65 years), drugs or alcohol (1 point each) (where 'drugs/alcohol' refers to concomitant use of drugs such as antiplatelet agents, NSAIDs, or alcohol abuse, etc.).
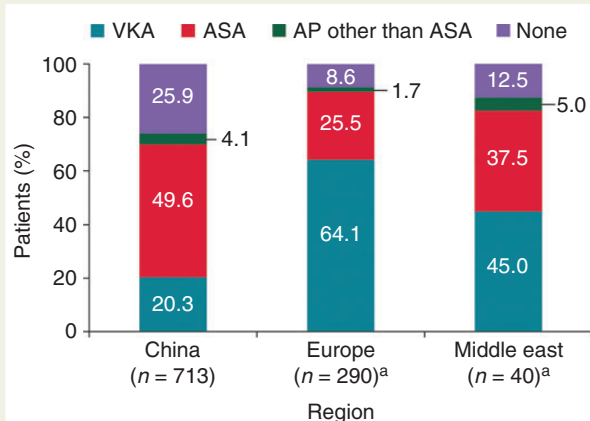

Figure 2 Antithrombotic treatment pattern by region (all regions). [a]One patient from Europe and 19 from the Middle East are excluded due to receipt of NOAC. AP, antiplatelet agents.
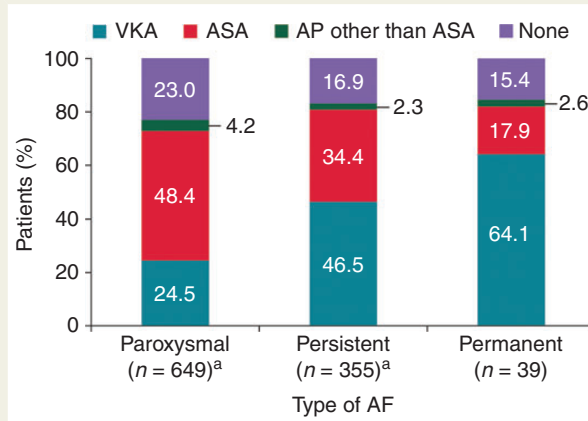

Figure 3 Antithrombotic treatment pattern by AF type (all regions). [a]Sixteen patients with paroxysmal AF and four with permanent AF are excluded from the graph because they received a NOAC.

appendix). The univariable logistic regression results are shown in *Table A2* in the appendix. Patients with prior ablation or prior non-CNS arterial embolism or who were from Europe were more likely to be prescribed VKAs. Patients taking antiplatelets and/or NSAIDs and patients with hepatic disease were less likely to be prescribed VKAs. Atrial fibrillation ablation, non-CNS arterial embolism, and hepatic disease are rare conditions, with a prevalence of <4% in the study cohort; thus, they have a limited predictive value for VKA use in general.

Reasons to forego vitamin K antagonists

For the 694 eligible patients receiving neither VKAs nor combinations of VKAs, the most frequent reason to forego VKAs was that the patient was currently in stable sinus rhythm. Other frequent,

specific reasons to forego VKAs were an expected low stroke risk and patient's unwillingness to take VKAs.

Of the 139 total patients for whom perceived low stroke risk was given as the reason to forego VKA therapy, 35.3% (49) actually had low $CHADS_2$ scores, 58.3% (81) had moderate $CHADS_2$ scores, and 6.5% (9) had high $CHADS_2$ scores. These trends were similar for European and Chinese patients. For the CHA_2DS_2-VASc, this corresponds overall to 75.5% (105) patients with moderate CHA_2DS_2-VASc scores, and 24.5% (34 patients) with high CHA_2DS_2-VASc scores within the group of patients with perceived low stroke risk. In all regions, moderate CHA_2DS_2-VASc scores were predominant among those perceived as having low stroke risk [China, 82.5% (80/97); Europe, 58.5% (24/41); the Middle East, 100% (1/1)]. Many of
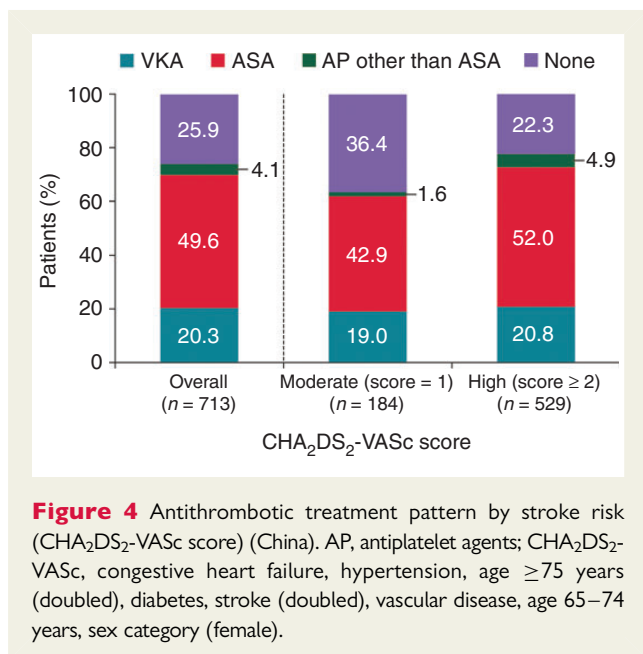
Figure 4 Antithrombotic treatment pattern by stroke risk (CHA$_2$DS$_2$-VASc score) (China). AP, antiplatelet agents; CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age $\geq$75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, sex category (female).

these patients had a CHA$_2$DS$_2$-VASc score of 1, defined by female gender alone, which may explain why some were considered low risk.

Reasons to forego vitamin K antagonists in patients with high stroke risk

For the 349 patients with high CHADS$_2$ scores (score $\geq$2) receiving neither VKAs nor combinations of VKAs, the most frequent reasons to forego VKAs were patient currently in stable sinus rhythm (22.6%; 79) and the non-specific 'other' category (39.8% of non-VKA patients; 139). As expected, only for nine patients out of the group of patients with CHADS$_2$ score $\geq$2, an expected low stroke risk was reported as reason to forgo VKA therapy. Within the subset of patients with CHADS$_2$ score $\geq$2, an expected high bleeding risk led to the decision to forgo VKA therapy in 44/349 patients. Thereby, in patients at high risk for stroke, investigators considered the bleeding risk to warrant withholding VKA therapy for 12.6% of these patients.

When using CHA$_2$DS$_2$-VASc instead of CHADS$_2$ to describe patients' stroke risk, similar results were observed; for the 516 patients with high CHA$_2$DS$_2$-VASc scores receiving neither VKAs nor combinations of VKAs, the most frequent reasons to forego VKAs were patient currently in stable sinus rhythm (25.8%; 133) and the non-specific 'other' category (38.4%; 198). Within the subset of patients with a high score, an expected high bleeding risk led to the decision to forgo VKA therapy in 47/516 patients (9.1%).

Discussion

The main objective of Phase I of the GLORIA-AF Registry Programme was to gather information on demographic and disease characteristics, as well as regional prescribing practices for treatment of NVAF during a time period before the availability of NOACs for the prevention of stroke in patients with AF. Therefore, patient enrolment for this phase of the programme stopped with the approval of the first NOAC (dabigatran) for this indication in a country.

In summary, Phase I enrolled 1063 eligible patients in China, The Netherlands, Spain, Germany, Croatia, Egypt, Lebanon, Turkey, and the United Arab Emirates. The majority of patients ($\sim$70%) were enrolled in China.

The observed patient demographics and medical history are reflective of a newly diagnosed patient population at risk of stroke with a median age of 70 years (IQR, 61.0–77.0) and multiple co-morbidities (*Table* 2). Overall, treatment with ASA was the most common (41.7%), followed by VKAs (32.8%) and no antithrombotic treatment (20.2%). Despite the fact that the majority of patients overall had moderate or high stroke risk and low bleeding risk, a substantial proportion of patients were not given any therapy. Patients with high CHADS$_2$ risk comprised the majority of patients in all groups that received treatment: 61.3% on VKA treatment, 56.7% on ASA treatment, and 75.0% on antiplatelet agents other than ASA. Similarly, by CHA$_2$DS$_2$-VASc score, patients with high stroke risk comprised the majority of patients in all groups: 86.5% on VKA treatment, 77.9% on ASA treatment, 88.9% on antiplatelet agents other than ASA, and 64.7% on no antithrombotic treatment. Overall, the majority of patients had a low bleeding risk, but patients with a high bleeding risk were more prevalent in the group of ASA-treated patients (19.6%) than in the group of VKA-treated patients (4.6%) and in patients not prescribed any antithrombotic therapy (0%).

There are two important reasons for the low number of patients on VKAs and the higher number on ASA in China. First, anticoagulation therapy is not commonly given to Asian patients with NVAF, probably because of the risk of critical bleeding during treatment, which has been reported to be higher among Asian patients. Warfarin-related intracranial haemorrhage in Asian patients was reported to be 1.75/100 patient-years, which is considerably higher than that in Caucasian patients (0.34/100 patient-years).[15] The second reason is that in China, many patients lack access to good laboratory control for VKA therapy and are therefore not prescribed VKAs. Of note, the percentage of patients on VKA therapy in China in our present study—20.3%—is strikingly higher than that in earlier community-based cohort studies in China that found between 0.5 and 2.7%.[16,17] This difference may reflect the fact that most patients in the current study were recruited in (university) hospital settings, with better access to healthcare resources, including warfarin control.[16,17]

Our findings are consistent with a recent report based on claims data showing that ASA use is increasing among newly diagnosed Chinese AF patients, with no relationship to the patient's stroke or bleeding risks, and that warfarin use was very low.[18] The suboptimal use of thromboprophylaxis in China has important implications given the increasing prevalence, incidence, and burden of AF in this region.[18]

Several other aspects of this study deserve comment. First, the most relevant predictors for VKA use based on logistic regression analyses were AF ablation, region, any drugs causing bleeding (i.e. antiplatelet agents and/or NSAIDs), non-CNS arterial embolism, and hepatic disease. Patients with prior ablation or prior non-CNS arterial embolism or who were from Europe were more likely to be prescribed a VKA. Specifically, patients taking antiplatelet agents and/or NSAIDs and patients with hepatic disease were less likely to be prescribed a VKA. Second, VKA initiation differed by type of site and regions since patients enrolled in Europe were more likely to be prescribed a VKA than patients enrolled in China, and patients enrolled at specialists' offices or university hospitals were

more likely to be prescribed a VKA than patients enrolled at general practice/primary care centres. Third, all three risk scores—HAS-BLED, CHADS$_2$, and CHA$_2$DS$_2$-VASc—were associated in univariable logistic regression analyses with VKA use, and the risk profile of a patient is an important factor for prediction of VKA use. Expected high bleeding risk was rarely reported by physicians as the rationale for foregoing treatment with VKAs. Importantly, despite the fact that the majority of patients were classified as having high stroke risk and low bleeding risk, approximately one in five patients remained untreated with thromboprophylaxis, especially in China. A shift to more VKA use in patients with AF was seen when 'going West'. Finally, there was lower VKA use in those with paroxysmal AF, indicating discrepancies between VKA use in clinical practice and guideline recommendations.

Limitations

There are limitations with the interpretation of these data based on the relatively small study size, especially for the Middle East, and the high representation of patients from China in the overall study population. As the end of Phase I was determined by the approval of dabigatran, the early approval in some countries led to a lower country participation and patient number than originally expected for this phase of the registry programme. Of the participating countries, China was the last country to approve dabigatran, which led to the high representation of Chinese patients in the study. The impact of the introduction of NOACs will be further explored in Phases II and III of GLORIA-AF, to assess treatment patterns after the availability of these agents. Data on variables, including patient educational level, economical class, patient mental condition, and patient living condition, i.e. if they were from urban or rural areas, were not available. The majority of patients (95.2%) were entered by cardiologists, which may have affected the population of the registry.

Conclusion

Phase I of GLORIA-AF demonstrated a wide variety of antithrombotic treatment patterns, depending on region. These geographical differences existed in the use of VKA therapy in the era before the availability of NOACs, with a notably lower use of VKAs in China.

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Appendix

Table A1 Association between patient characteristics and the decision to forego VKA based on multivariable logistic regression analysis

Variable	OR[a,b]	95% CI[a]	Odds of being prescribed treatment with VKA
Any drug (HAS-BLED)	0.066	(0.0391−0.1058)	Lower for patients on any antiplatelet medication, COX-2 inhibitor, or other NSAID
AF ablation	24.342	(7.9997−85.7171)	Higher for patients with AF ablation
Type of AF			
Paroxysmal	1.0	−	Higher for patients with persistent or permanent AF than for those with paroxysmal AF
Persistent	3.141	(2.0336−4.8950)	
Permanent	1.374	(0.4011−4.5970)	
Region			
China	1.0	−	Higher in patients in Europe or the Middle East relative to patients in China
Europe	14.683	(7.4549−30.0002)	
Middle East	3.275	(0.8056−12.5629)	
Type of site where patients treated			
GP/primary care	1.0	−	Lower for patients treated at community hospitals or other sites than at GP/primary care sites; higher for patients treated at specialists' offices or university hospitals
Specialists' offices	3.603	(1.4065−9.4857)	
Community hospitals	0.435	(0.0317−3.9350)	
University hospital	3.240	(1.5571−7.1283)	
Other sites	0.537	(0.0936−2.9496)	
Hypertension			
No	1.0	−	Higher for patients with either uncontrolled or controlled hypertension
Yes, uncontrolled	1.453	(0.5901−3.4937)	
Yes, controlled	2.206	(1.3325−3.7161)	
Pacemaker	0.230	(0.0484−0.8962)	Lower for patients with pacemaker
Congestive heart failure	1.691	(1.0379−2.7550)	Higher for patients with congestive heart failure
Hepatic disease	0.086	(0.0032−0.8791)	Lower for patients with hepatic disease
Antihypertensive/heart failure and antiarrhythmic therapy	1.645	(1.0298−2.6516)	Higher for patients on antihypertensive/heart failure and antiarrhythmic therapy
Diabetes mellitus	1.654	(1.0045−2.7231)	Higher for patients with diabetes mellitus
Smoking status			
Non-smoker	1.0	−	Lower for patients who are current smokers, and higher for patients who are past smokers, than for those who are non-smokers
Current smoker	0.534	(0.2751−1.0038)	
Past smoker	1.405	(0.7787−2.5214)	
Hyperlipidaemia	1.667	(0.9798−2.8354)	Higher for patients with hyperlipidaemia
Non-CNS arterial embolism	12.860	(0.8195−325.3468)	Higher for patients with non-CNS arterial embolism

AF, atrial fibrillation; CI, confidence interval; CNS, central nervous system; GP, general practitioner; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; VKA, vitamin K antagonist.
[a]From likelihood ratio test.
[b]If not specified differently, OR are for presence vs. absence of patient characteristic.

Table A2 Association between patient characteristics and the decision to prescribe VKA based on univariable logistic regression analysis

Variable	OR[a,b]	95% CI[b]	Odds of being prescribed treatment with VKA
HAS-BLED risk score ≥ 3	0.305	(0.1705–0.5125)	Lower for patients with high bleeding risk (score ≥ 3)
CHADS$_2$ score class			
Low risk	1.0	–	Higher for patients with moderate or higher stroke risk than for those with
Moderate risk	2.959	(1.6659–5.6219)	lower stroke risk
High risk	3.854	(2.2063–7.2283)	
CHA$_2$DS$_2$-VASc score class, score ≥ 2	2.217	(1.5717–3.1782)	Higher for patients with higher stroke risk than for those with moderate stroke risk
AF ablation	6.671	(3.2324–15.1401)	Higher for patients with AF ablation
Type of AF			
Paroxysmal	1.0	–	Higher for patients with persistent or permanent AF than for those with
Persistent	2.676	(2.0347–3.5261)	paroxysmal AF
Permanent	5.503	(2.8313–11.1139)	
Any drug (HAS-BLED)	0.167	(0.1249–0.2211)	Lower for patients on any antiplatelet medication, COX-2 inhibitor, or other NSAID
LVH	2.214	(1.5265–3.2119)	Higher for patients with LVH
Hyperlipidaemia	2.111	(1.5675–2.8433)	Higher for patients with hyperlipidaemia
Weight class, kg			
<50	1.0	–	Higher for patients in weight class 50 to <100 or ≥ 100 kg
50 to <100	2.688	(1.3662–5.9207)	
≥ 100	8.205	(3.1245–23.2589)	
BMI class, kg/m$_2$			
18.5 to <25	1.0	–	Lower for patients with BMI <18.5 than for those with BMI 18.5 to <25
<18.5	0.450	(0.1512–1.0812)	Higher for patients with BMI ≥ 25 than for those with BMI 18.5 to <25
25 to <30	1.760	(1.3138–2.3624)	
30 to <35	3.614	(2.3960–5.4769)	
≥ 35	5.085	(1.9985–3.9435)	
Alcohol use			
No alcohol	1.0	–	Higher for patients who consumed <1–1–7, or ≥ 8 drinks/week than for
<1 drink/week	2.506	(1.7352–3.6213)	those who consumed no alcohol
1–7 drinks/week	1.476	(1.0245–2.1129)	
≥ 8 drinks/week	2.577	(0.7970–8.3315)	
Race			
White	1.0	–	Lower for patients who were not white
Asian	0.143	(0.1057–0.1924)	
Arab/Middle East	0.349	(0.1590–0.7387)	
Region			
China	1.0	–	Higher for patients in Europe or the Middle East than for patients in China
Europe	7.006	(5.1970–9.4997)	
Middle East	3.205	(1.6576–6.1258)	
Type of site where patients were treated			
GP/primary care	1.0	–	Lower for patients treated at community hospitals than at GP/primary care sites;
Specialists' offices	3.655	(2.1491–6.3601)	higher for patients treated at specialists' offices or other sites
Community hospitals	0.159	(0.0246–0.5771)	
University hospital	1.004	(0.6268–1.6494)	
Other sites	4.569	(1.4410–16.0961)	
History of hypertension	1.841	(1.3479–2.5412)	Higher for patients with hypertension
Hypertension			
No	1.0	–	Higher for patients with either uncontrolled or controlled hypertension
Yes, uncontrolled	1.322	(0.7582–2.2616)	
Yes, controlled	1.896	(1.3807–2.6287)	

Continued

Table A2 *Continued*

Variable	OR[a,b]	95% CI[b]	Odds of being prescribed treatment with VKA
CAD	0.549	(0.3950−0.7551)	Lower for patients with CAD
Any prior VKA therapy during lifetime	4.121	(1.7937−10.2542)	Higher for patients with prior VKA therapy during lifetime
Chronic gastrointestinal diseases	0.386	(0.1951−0.7019)	Lower for patients with chronic gastrointestinal diseases
Neurologic disease	3.490	(1.3908−9.4516)	Higher for patients with neurologic disease
PAD	4.090	(1.4414−13.2177)	Higher for patients with PAD
Antihypertensive/heart failure and antiarrhythmic therapy	1.464	(1.1017−1.9563)	Higher for patients on antihypertensive/heart failure and antiarrhythmic therapy
Any chronic concomitant medication	1.469	(1.0844−2.0073)	Higher for patients on any chronic concomitant medication
Previous stroke timing			
No	1.0	−	Higher for patients with recent or past stroke
Recent	2.919	(1.3881−6.3422)	
Past	1.190	(0.6072−2.2515)	
Smoking status			
Non-smoker	1.0	−	Lower for patients who are current smokers and higher for patients who are past smokers than for those who are non-smokers
Current smoker	0.595	(0.3863−0.8954)	
Past smoker	1.168	(0.8097−1.6740)	
Angina pectoris	0.639	(0.4174−0.9559)	Lower for patients with angina pectoris
Diabetes mellitus	1.401	(1.0348−1.8922)	Higher for patients with diabetes mellitus
Non-CNS arterial embolism	8.034	(1.1832−157.3896)	Higher for patients with non-CNS arterial embolism
Pacemaker	0.356	(0.1034−0.9382)	Lower for patients with a pacemaker
Congestive heart failure	1.360	(1.0119−1.8228)	Higher for patients with congestive heart failure
Other concomitant drugs	1.402	(1.0117−1.9338)	Higher for patients on other concomitant drugs
Creatinine clearance class 1, ml/min			
<30	1.0	−	Higher for patients with creatinine clearance ≥30
30 to <50	1.061	(0.4368−2.8641)	
50 to <80	1.754	(0.7726−4.5149)	
≥80	1.940	(0.8482−5.0188)	
Physician specialty	1.879	(0.9853−3.8913)	Higher for patients treated by cardiologists
Categorization of AF			
Symptomatic	1.0	−	Higher for patients with minimally and asymptomatic AF
Minimally symptomatic	1.164	(0.8421−1.6003)	
Asymptomatic	1.523	(1.0723−2.1565)	
Psychosocial factors	3.014	(0.8564−11.8664)	Higher for patients with psychosocial factors
Gender	1.247	(0.9633−1.6143)	Higher for female patients
DVT	4.029	(0.7826−29.1577)	Higher for patients with DVT
Previous stroke	1.418	(0.9387−2.1248)	Higher for patients with previous stroke
MI	0.706	(0.4350−1.1142)	Higher for patients without MI
Age class[c], ≥80 years	0.763	(0.5269−1.0897)	Lower for younger patients <80 years
Age class 2			
<65 years	1.0	−	Higher for patients between 65 and <75 years
65 to <75 years	1.095	(0.7969−1.5028)	
≥75 years	0.886	(0.6502−1.2065)	
Hepatic disease	0.359	(0.0553−1.3461)	Higher for patients without hepatic disease
Metabolic and anti-inflammatory therapy	0.997	(0.7627−1.3009)	
Cancer	1.191	(0.6540−2.1133)	Higher for patients with cancer
Abnormal kidney function	0.626	(0.2263−1.4962)	Higher for patients without abnormal kidney function
Hyperthyroidism	1.347	(0.5234−3.2881)	Higher for patients with hyperthyroidism
Pulmonary embolism	3.014	(0.4979−22.9857)	Higher for patients with pulmonary embolism
TIA	1.337	(0.5760−2.9764)	Higher for patients with TIA
Cardioversion	1.230	(0.8637−1.7390)	Higher for patients with cardioversion

Table A2 *Continued*

Variable	OR[a,b]	95% CI[b]	Odds of being prescribed treatment with VKA
Presence of complex aortic plaque			
No	1.0	–	Higher for patients with presence of complex aortic plaque
Yes	1.817	(0.6505−4.8058)	
Not applicable	1.183	(0.8406−1.6540)	
After AF diagnosis bleeding	1.498	(0.2938−6.8292)	Higher for patients with AF diagnosis after bleeding
Before AF diagnosis bleeding	0.724	(0.2998−1.5809)	Lower for patients with AF diagnosis before bleeding

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CNS, central nervous system; DVT, deep vein thrombosis; GP, general practitioner; LVH, left ventricular hypertrophy; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; PAD, peripheral arterial disease; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

[a]From likelihood ratio test.

[b]If not specified differently, OR are for presence vs. absence of patient characteristics.

[c]Not assessed for inclusion in multivariable model; for age, it was pre-specified to include the age classification ($<$65, 65 to $<$75, $\geq$75 years).